AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph starting on page 1, line 36 and ending on page 2, line 7 with the following paragraph:

FVIII is a protein which is so complex that, even though the sequence of its gene has been known since 1984 (~~Verhar~~ Vehar et al. 1984 Nature 312, pp. ~~317~~ 337-342), neither the complete structure of plasma FVIII (only about 50% of the protein has been sequenced) nor the precise structure of the carbohydrates has yet been established. The DNA sequence has been allowed to define the primary sequence of FVIII (SEQ ID NO: 21) (a rare exception to the instructions laid down by the FDA for the therapeutic products derived from biotechnology).

Please replace the paragraph on page 16, lines 3-7 of the Specification as filed with the following paragraph:

- the epitope contained between aspartic acid ~~2018~~ 2108 and glycine 2121, defined by the following sequence: SEQ ID NO: 19:

```
Asp Gly Lys Lys Trp Gln Thr Tyr Arg Gly Asn Ser Thr Gly
 1               5                  10
```

AMENDMENTS TO THE SEQUENCE LISTING

Please replace the original Sequence Listing with the accompanying Substitute Sequence Listing. **SEQ ID NO: 5** has been amended to recite Asp 1795 instead of Asn 1795 as was originally filed in the PCT application, and to include the amino acids that were inadvertedly omitted in the Sequence Listing as originally filed in this Application. Support for the amendments can be found in the Specification as filed on page 12, lines 25-28. **SEQ ID NO: 13** has been amended to include the amino acids that were inadvertedly omitted in the Sequence Listing as originally filed in this Application. Support for the amendment can be found in the Specification as filed on page 14, lines 21-24. **SEQ ID NO: 17** has been amended to recite Glu720 instead of Gly720. Support for the amendment can be found in the deduced Factor VIII amino acid sequence as published in Vehar et al. 1984 Nature 312, pp. 337-342 referred to in the Specification as filed on page 1, line 38, and now presented as **SEQ ID NO: 21** per the Examiner's request. Therefore, no new matter has been introduced with these amendments.

AMENDMENTS TO THE CLAIMS

1-30. **Cancelled**

31. **(Currently Amended)** An antigenic fragment of the human Factor VIII polypeptide of SEQ ID NO: 21, said fragment comprising at least 7 amino acids of a human Factor VIII fragment selected from the group consisting of a human Factor VIII fragment ~~contained between~~ extending from arginine 1652 ~~and~~ to arginine 1696 inclusive, a human Factor VIII fragment extending from threonine 1739 to tyrosine 1748 inclusive (SEQ ID NO: 3), a human Factor VIII fragment extending from asparagine 1777 to phenylalanine 1785 inclusive (SEQ ID NO: 4), ~~a human Factor VIII fragment contained between threonine 1739 and aspartic acid 1831 inclusive~~, and a human Factor VIII fragment ~~contained between~~ extending from glutamic acid 1885 ~~and~~ to arginine 1917 inclusive.

32. **(Currently Amended)** The antigenic polypeptide according to Claim 31, wherein said human Factor VIII fragment comprises an epitope selected from the group consisting of: a human Factor VIII fragment ~~contained between~~ extending from arginine 1652 ~~and~~ to tyrosine 1664 (SEQ ID No: 1), a human Factor VIII fragment ~~contained between~~ extending from threonine 1739 ~~and~~ to tyrosine 1748 (SEQ ID No: 3), a human Factor VIII fragment ~~contained between~~ extending from asparagine 1777 ~~and~~ to phenylalanine 1785 (SEQ ID No: 4), ~~a human Factor VIII fragment contained between glutamic acid 1794 and tyrosine 1815 (SEQ ID No: 5), a human Factor VIII fragment contained between methionine 1823 and aspartic acid 1831 (SEQ ID No: 6),~~ a human Factor VIII fragment ~~contained between~~ extending from glutamic acid 1885 ~~and~~ to phenylalanine 1891 (SEQ ID No: 7), a human Factor VIII fragment ~~contained between~~ extending from glutamic acid 1893 ~~and~~ to alanine 1901 (SEQ ID No: 8), and a human Factor VIII fragment ~~contained between~~ extending from aspartic acid 1909 ~~and~~ to arginine 1917 (SEQ ID No: 9).

33. **(Previously Presented)** The antigenic polypeptide according to Claim 31, wherein said antigenic polypeptide comprises tyrosine or histidine.

34. **(Currently Amended)** A conformational epitope ~~containing~~ comprising at least two different human Factor VIII fragments of Claim 32, wherein said fragments are positioned in proximity to each other when the protein is folded in its tertiary or quaternary structure to form a conformational epitope which is recognized by an inhibitor of Factor VIII selected from the

group consisting of B lymphocytes, MHC I proteins, MHC II proteins, and anti-Factor VIII antibodies.

35. **(Currently Amended)** A conformational epitope ~~containing~~ comprising at least two different epitopes from a ~~human Factor VIII fragment~~ fragment of the human Factor VIII polypeptide of SEQ ID NO: 21 wherein said fragment is selected from the group consisting of a human Factor VIII fragment ~~contained between~~ extending from arginine 1652 ~~and~~ to arginine 1696 inclusive, a human Factor VIII fragment ~~contained between~~ extending from threonine 1739 ~~and~~ to aspartic acid 1831, inclusive, and a human Factor VIII fragment ~~contained between~~ extending from glutamic acid 1885 ~~and~~ to arginine 1917 inclusive.

36. **(Currently Amended)** A complex, comprising a carrier protein or a carrier peptide linked to the ~~antigenic~~ polypeptide of Claim 31 or the conformational epitope of Claim 35, ~~whereby~~ wherein said complex ~~increases~~ has higher immunogenicity than said polypeptide of Claim 31.

37-38. **(Cancelled)**

39. **(Previously Presented)** A pharmaceutical composition comprising at least the antigenic polypeptide of Claim 31, or the conformational epitope of Claim 35 and an acceptable pharmaceutical vehicle.

40-43. **(Canceled)**

44. **(New)** The complex of Claim 36, wherein said carrier protein or said carrier peptide are bovine serum albumin or hemocyanin.

45. **(New)** A polypeptide, consisting of a fragment of the human Factor VIII polypeptide of SEQ ID NO: 21, wherein said fragment is selected from the group consisting of a human Factor VIII fragment between arginine 1652 and arginine 1696 inclusive, a human Factor VIII fragment between threonine 1739 and aspartic acid 1831 inclusive, and a human Factor VIII fragment between glutamic acid 1885 and arginine 1917 inclusive, and a fragment comprising at least 7 amino acids thereof, wherein said polypeptide is antigenic.

46. **(New)** A pharmaceutical composition, comprising the antigenic polypeptide of Claim 45 and an acceptable pharmaceutical vehicle.

47. **(New)** A complex, comprising a carrier protein or a carrier peptide linked to the antigenic polypeptide of Claim 45, wherein said complex has higher immunogenicity than said polypeptide of Claim 45.

48. **(New)** The complex of Claim 47, wherein said carrier protein or said carrier peptide are bovine serum albumin or hemocyanin.

49. **(New)** A conformational epitope comprising at least two different human Factor VIII fragments of Claim 45, wherein said fragments are positioned in proximity to each other when the protein is folded in its tertiary or quaternary structure to form a conformational epitope which is recognized by an inhibitor of Factor VIII selected from the group consisting of B lymphocytes, MHC I proteins, MHC II proteins, and anti-Factor VIII antibodies.

50. **(New)** The polypeptide according to Claim 45, wherein said human Factor VIII fragment consists of an epitope selected from the group consisting of: a human Factor VIII fragment contained between arginine 1652 and tyrosine 1664 (SEQ ID No: 1), a human Factor VIII fragment contained between threonine 1739 and tyrosine 1748 (SEQ ID No: 3), a human Factor VIII fragment contained between asparagine 1777 and phenylalanine 1785 (SEQ ID No: 4), a human Factor VIII fragment contained between glutamic acid 1794 and tyrosine 1815 (SEQ ID No: 5), a human Factor VIII fragment contained between methionine 1823 and aspartic acid 1831 (SEQ ID No: 6), a human Factor VIII fragment contained between glutamic acid 1885 and phenylalanine 1891 (SEQ ID No: 7), a human Factor VIII fragment contained between glutamic acid 1893 and alanine 1901 (SEQ ID No: 8), and a human Factor VIII fragment contained between aspartic acid 1909 and arginine 1917 (SEQ ID No: 9).

51. **(New)** A pharmaceutical composition, comprising the antigenic polypeptide of Claim 50 and an acceptable pharmaceutical vehicle.

52. **(New)** A complex, comprising a carrier protein or a carrier peptide linked to the antigenic polypeptide of Claim 50, wherein said complex has higher immunogenicity than said polypeptide of Claim 45.

53. **(New)** The complex of Claim 52, wherein said carrier protein or said carrier peptide are bovine serum albumin or hemocyanin.

54. **(New)** A conformational epitope comprising at least two different human Factor VIII fragments of Claim 50, wherein said fragments are positioned in proximity to each other

when the protein is folded in its tertiary or quaternary structure to form a conformational epitope which is recognized by an inhibitor of Factor VIII selected from the group consisting of B lymphocytes, MHC I proteins, MHC II proteins, and anti-Factor VIII antibodies.

REMARKS

The Specification has been amended to correct typographical errors and to include the SEQ ID NO for the sequence of the human Factor VIII protein. Support for the amendment can be found in the Specification as filed on page 1, line 38. Therefore, no new matter has been introduced.

The Sequence Listing has been amended. Support for the amendments can be found in the Specification as filed and in the published amino acid sequence of human Factor VIII. Therefore, no new matter has been introduced with the amendments.

Claims 31, 32, 34, 35 and 36 have been amended. Claims 40-43 have been canceled. New Claims 44 - 54 have been added. Therefore, Claims 31-36, 39, and 44-54 are now pending. The Support for the new Claims 44, 48 and 53 can be found in the Specification as filed (page 18, lines 31-36). Support for the new Claims 45, 46, 47, 50, 51 and 52 can be found in the Claims 31, 32, 36 and 39. Support for the new claims 49 and 54 can be found in Claims 34 and 35. No new matter has been introduced herewith. The following addresses the substance of the current Office Action.

Claim rejections under 35 U.S.C. §102

The Examiner has maintained his rejection of Claims 31-34, 36 and 39 under 35 U.S.C. §102(b) over Capon *et al.* (US 4,965,199). More specifically, the Examiner asserts that Claims 31-34, 36 and 39 are unpatentable over the fragment 1799-1860 of human Factor VIII in '199 patent because they recite a fragment of human Factor VIII between the amino acids 1739 and 1831. The Applicants have amended Claims 31 and 32 to specifically exclude such fragment. Therefore, the Applicants respectfully assert that the now amended Claims 31-34, 36 and 39 are patentable over Capon et al.

With respect to new Claims 45 - 54, Applicants note that they include the human Factor VIII fragment between amino acids 1739 and 1831 (Claims 45- 48), fragments between amino acids 1794 and 1815 (Claim 50-54) and fragments between amino acids 1823 and 1831 (Claims 50-54). With respect to the fragment between amino acids 1739 and 1831 recited in Claim 45, Applicants maintain that this fragment is not anticipated by the disclosure of the fragment between amino acid 1799 and amino acid 1860 in Capon because the claimed fragment does not

encompass the full fragment disclosed in Capon but instead includes amino terminal residues not included in the fragment disclosed in Capon and is truncated at the carboxy terminus relative to the fragment disclosed in Capon. Applicant further maintains that one skilled in the art would not appreciate that the claimed fragment was immunogenic based on the disclosure in Capon and that prior to Applicants discovery that the fragment was in fact immunogenic, there was no suggestion in the cited reference that the claimed fragment is immunogenic.

With respect to the fragment between amino acids 1794 and 1815 recited in Claim 50, Applicants note that a portion of the fragment includes amino terminal residues not included in the fragment disclosed in Capon and is truncated at the carboxy terminus relative to the fragment disclosed in Capon. Applicant further maintains that one skilled in the art would not appreciate that the claimed fragment was immunogenic based on the disclosure in Capon and that prior to Applicants discovery that the fragment was in fact immunogenic, there was no suggestion in the cited reference that the claimed fragment is immunogenic.

With respect to the fragment between amino acids 1823 and 1831 recited in Claim 50, Applicants maintain that, although this fragment is included in the fragment disclosed in Capon, as discussed above there was no teaching or suggestion in Capon that this subfragment is immunogenic.

For the foregoing reasons, Applicants maintain that the claims are patentable over the cited references.

Claim 36 was amended to clarify that the complex has a greater level of immunogenicity than the polypeptides of Claim 31. Support for the amendment can be found in the Specification as filed (page 18, lines 31-36).

Allowable subject matter

The Examiner has indicated that Claim 35 is allowed.

Teleconference with Examiner

The Applicant wishes to thank the Examiner for contacting the undersigned as requested in the Amendment After Final Office Action to advise him that the Amendment would not be entered because it raised new issues and to point out certain formalities that could be addressed in the present Amendment in order to expedite prosecution of the application.

As suggested by the Examiner, Applicants have amended the Sequence Listing to include the human Factor VIII polypeptide sequence as SEQ ID NO: 21. The claims have also been amended to recite that the claimed fragments are fragments of the polypeptide of SEQ ID NO: 21.

Applicants note that the accepted sequence of the human Factor VIII polypeptide is provided in the Vehar publication referenced on page 1 of the present specification. Accordingly, Applicants maintain that no new matter has been introduced by these amendments.

The Examiner also suggested that the terms "contained" and "containing" in the claims be replaced with terminology that is standard under U.S. practice. The Applicant has amended Claims 31, 32, 34 and 35 to now recite "comprising" and "extending from" in appropriate instances.

Applicants believe that all outstanding issues in this case have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Aug 22, 2003

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 20,995
(619) 235-8550

O:\DOCS\MXG\MXG-3169.DOC
072303